

Gene networks from DNA microarray data: centrality and lethality

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Abstract

We construct a gene network based on expression data from DNA microarray experiments, by establishing a link between two genes whenever the Pearson's correlation coefficient between their expression profiles is higher than a certain cutoff. The resulting connectivity distribution is compatible with a power-law decay with exponent $\gamma \sim 1$, corrected by an exponential cutoff at large connectivity. The biological relevance of such network is demonstrated by showing that there is a strong statistical correlation between high connectivity number and lethality: in close analogy to what happens for protein interaction networks, essential genes are strongly overrepresented among the hubs of the network, that is the genes connected to many other genes.

DNA microarray experiments are one of the most powerful tools for studying interactions between genes on the scale of the whole genome. It is widely believed that a huge amount of biologically relevant information is encoded in the results of such experiments, and that new analytical methods need to be developed to extract it.

In this work we propose to analyse the expression data obtained in microarray experiments by constructing a network of coregulated genes: the genes are the nodes of the network, and a link is established between two nodes whenever they are similarly expressed across many experimental conditions. On one hand, we show that such network, like many other known networks of self-organizing origin, shows a connectivity distribution that decays with a power law corrected, for large values of the connectivity, by an exponential cutoff [1, 2]. On the other hand, we show that the network encodes biologically relevant information in

its topology: exactly as in the case of the protein interaction network in yeast [3], centrality is strongly correlated to lethality. In other words, among the genes that have the highest connectivity in the network, essential genes, whose deletion produces an inviable mutant, are strongly overrepresented.

We will work on yeast (*S. cerevisiae*), and use the expression data made publicly available by the authors of Ref.[4] (and that include also the data obtained by the authors of Ref.[5]), who performed a series of microarray experiments with the goal of identifying cell-cycle regulated genes. The data consist in the expression profiles for virtually all of the ~ 6200 yeast genes across a total of 77 timepoints.

The network is constructed by the following procedure:

1. To each gene we associate its expression profile defined as a string of 77 real numbers, representing as it is customary the \log_2 of the ratio between expression (quantity of mRNA) at the given time-point and a reference value of the expression. The data come from different experiments and have been processed by the authors of Ref.[4], to which we refer for details, so as to be comparable to each other across the various experiments.
2. Missing values are replaced with the average expression over the available timepoints. To prevent this manipulation from having a sizable effect on the construction of the network, we retain only those genes for which at least 70 timepoints out of 77 are available. We are thus left with 5293 genes as the nodes of our network.
3. We compute the Pearson's correlation coefficient r for all pairs of nodes in the network.
4. We establish a link between two nodes whenever r is larger than a certain cutoff C .

The only free parameter in the procedure is the cutoff C . A possible way of choosing it is to compare the probability distribution of r for the actual data to the same distribution after the data have been randomized by shuffling the expression values of each gene. For the randomized data, no pair of genes shows a value of r greater than 0.67: therefore by choosing $C = 0.67$ the links we create can be considered of biological origin. A similar procedure was used in Ref.[6], where a network was constructed by establishing a link between two genes whenever the effects of their deletion on the expression of the rest of the genome were linearly correlated.

With this choice of the cutoff C , 17643 links are established between the genes. Defining the connectivity k of a node as the number of links departing from it, we have an average connectivity $\langle k \rangle \sim 6.67$. Defining $N(k)$ as the number of nodes with connectivity k , we see that $N(k)$ shows a long tail that reaches up to $k = 173$: the shape of the distribution is compatible with a power law decay with exponential cutoff:

$$N(k) = a k^{-\gamma} \exp\left(-\frac{k}{k_c}\right) \quad (1)$$

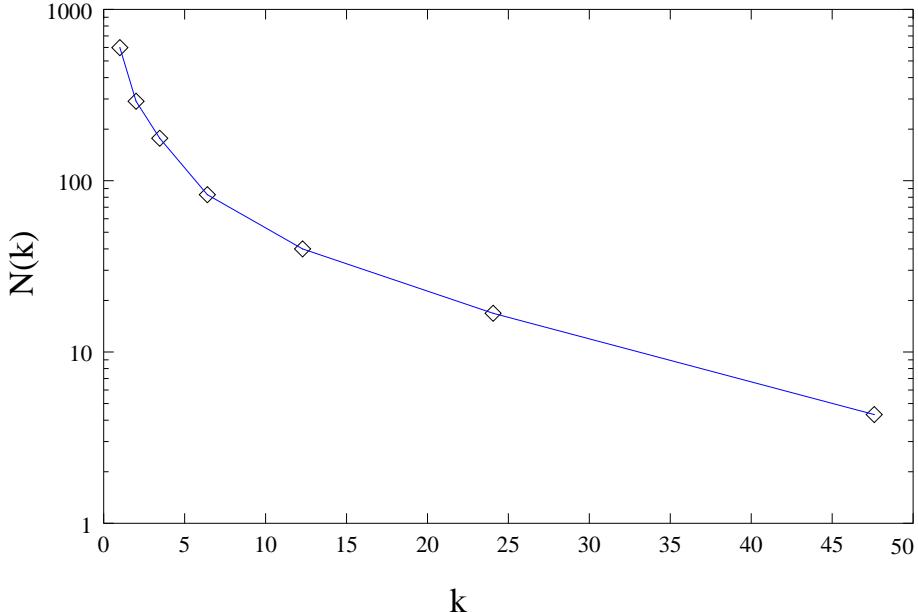


Figure 1: Linear-log plot of $N(k)$, the number of nodes with connectivity k , showing that the decay is slower than exponential.

This is shown in Figs. 1-3: Fig. 1 shows $N(k)$ in logarithmic scale as a function of k (noise in the data has been reduced by logarithmic binning), showing that the decay of $N(k)$ is slower than exponential for small to moderate values of k . Fig. 2 shows the same data with logarithmic scale on the k axis too, and demonstrates that the decay is faster, at large k , than the pure power law characteristic of scale-free networks. Finally Fig. 3 shows the data after correction with the exponential cutoff, with $k_c \sim 38$. The slope of the straight line is $\gamma = 0.95$. An analysis of the cumulative distribution confirms these results. Interestingly, a recent study of the transcriptional regulation network in yeast also revealed a scale-free network with $\gamma \sim 1$ [7].

In this paper, we are mainly concerned with establishing the biological relevance of this network, independently of any of its graph-theoretic features. This we will do by showing that the nodes in the network with high connectivity are more likely to be essential genes, whose deletion produces an inviable mutant.

A list of essential yeast genes is publicly available from the *Saccharomyces Genome Deletion Project* [8], and comprises 1104 genes, corresponding to 18.7% of the genes deleted in the project. Of the 5293 genes in our network, 964 (18.2%) are included in the list. Fig. 4 shows the fraction $f(k_{min})$ of essential genes among the genes having connectivity k_{min} or more, as a function of k_{min} : it grows from 0.182 at $k_{min} = 0$ (by definition) to 1 for the 6 most connected genes ($k \geq 155$).

The figure shows that essential genes are more and more overrepresented

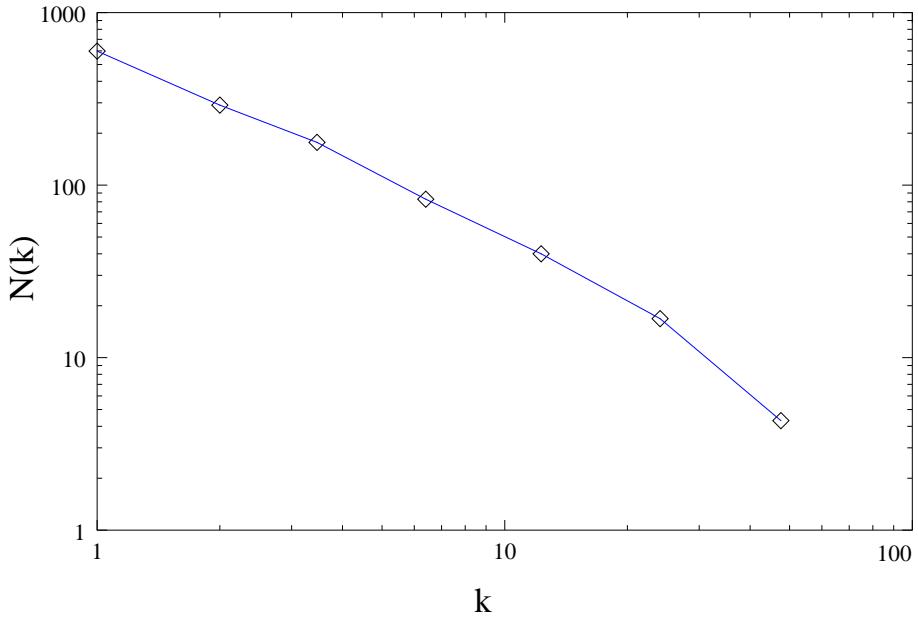


Figure 2: Log-log plot of $N(k)$, showing a power-like decay with an exponential cutoff at large distances.

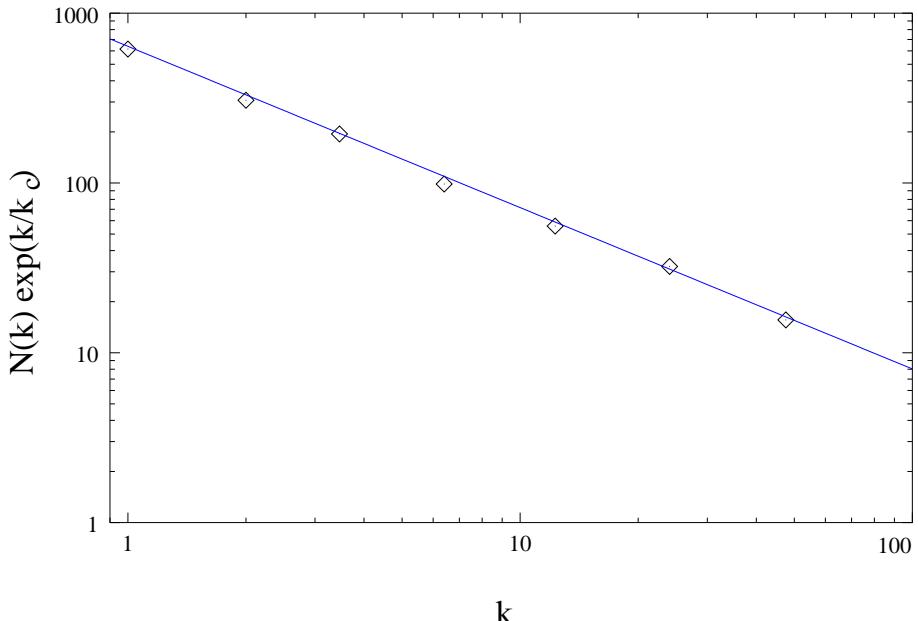


Figure 3: Log-log plot of $N(k)$ after correction with the exponential cutoff at $k_c \sim 37$. The slope of the straight line is ~ 0.95 .

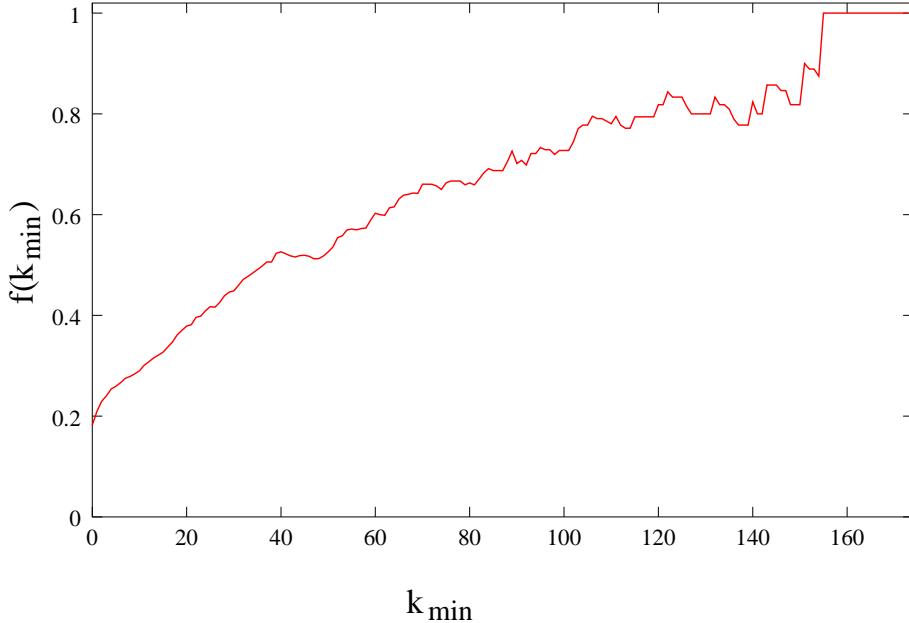


Figure 4: The fraction $f(k_{min})$ of essential genes among the ones with connectivity $k \geq k_{min}$.

as the minimum connectivity k_{min} is increased. To evaluate the statistical significance of such overrepresentation, suppose that the number of genes with connectivity $k \geq k_{min}$ is n , and that among these m are essential. Then one can evaluate the probability $P(N, M; n, m)$ that, out of n randomly chosen nodes out of a set of N , m or more are essential genes, when the total number of essential genes is M . This probability can be computed as the right tail of the appropriate hypergeometric distribution, and reaches very small values: for example the fraction of essential genes reaches 50% for $k_{min} = 37$, with $m = 127$ essential genes out of $n = 251$ nodes, and the probability $P(N = 5293, M = 964; n = 251, m = 127)$ is about $4 \cdot 10^{-33}$.

In conclusion, we have built a gene network based on expression data obtained with DNA microarray experiment, by joining genes showing similar expression profiles. The resulting network shows a power law decay of the connectivity distribution with an exponential cutoff, and exponent $\gamma \sim 1$. Its biological relevance is proved by the strong statistical correlation between centrality and lethality.

Acknowledgements. I would like to thank M. Caselle and C. Herrmann for many useful conversations and suggestions. I am also grateful to M. Barthélémy for many useful comments about a previous version of this manuscript.

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